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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,044	07/14/2005	Ralph Biemans	B45313	7576

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
03/27/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,044	BIEMANS ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14-20,53 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *15-20 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14 16-18 and 56-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election ***without*** traverse of Group I, species b) directed to Neisserial bleb preparation derived from an lgtB- neisserial strain with an L3 LOS immunotype (claims 1-10, 14 (only as it pertains to bleb) and 16-18) and wherein the capsular downregulated gene is siaD, in the reply filed on 1/4/08 is acknowledged. It is agreed that cancelled claims 9 and 10 are to be placed in new Group VII. With respect to the election of the single species of downregulated capsular polysaccharide gene, Applicants arguments concerning that this should be a species election and not a restriction requirement are persuasive. The initial species election, siaD, is acknowledged with the understanding that if one or more generic claims are found allowable, additional species which are dependent from or otherwise include all of the limitations of the allowed generic claim will be examined.

Claims 1-8, 14-20, 53 and new claims 56-58 are currently pending.

Claims 15-20 and 53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claims 1-8, 14, 16-18, and new claims 56-58 are currently under examination.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 is rejected under 35 U.S.C. 101 because he claimed invention is directed to non-statutory subject matter. The instant claim does not recite that the neisserial bleb preparation has been isolated and/or purified and therefore reads on a product of nature as these type of preparations with the indicated mutation can occur naturally. LOS is naturally occurring on Neisserial blebs.

Claim Rejections - 35 USC § 112-2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-8, 14, 16-18, and claims 56-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite due to the description 'an lgtB$^-$ neisserial strain' because it is unclear what this is in reference too. Do Applicants intend to imply that the lgtB$^-$ *gene* is absent or inactivated in some manner? The claim should expressly recite that it is a gene mutation. Clarification and correction is required.

Claim 1 is also vague and indefinite because it is unclear whether the L3 LOS is naturally occurring or conjugated to the bleb preparation. The specification does not clarify since it teaches that bleb preparation methods have the effect of removing most of the LOS antigen from the composition. See specification at page 3, lines 14-15. The instant claims do not require any specific extraction conditions which would prevent the loss of LOS antigen in the blebs. Additionally, dependent claims 14 and 15 teach the conjugation of the

LOS to the surface of the bleb so it is unclear if the bleb derived from 'a strain with an L3 LOS immunotype' as recited in claim 1 has the full LOS antigen or has loss most of it due to the preparation of the bleb. Claim 1 as written does not appear to suggest that the LOS has been conjugated to the bleb since the bleb is derived from a strain with a L3 LOS immunotype, thereby not even requiring the full L3 LOS structure to be present in the prepared product. The claim also does not teach that the LOS is non-toxic, as LOS is naturally toxic. Are toxic compositions intended to be included in the scope of the claim? Is the LOS conjugation in claims 14 and 15 in addition to any LOS remaining from the strain from which the LOS was derived? The metes and bounds of the claimed structure cannot be understood. Clarification and/or correction to the claim is required.

Claim 1 is also vague and indefinite due to the term 'derived'. The term "derived" does not provide the character or properties from the source that are to be retained in the final product, e.g., paper is derived from wood but is very different from wood. The phrase "derived from" should be changed to "isolated from". Clarification and correction is required.

Claims 4-7 are vague and indefinite because it is unclear whether it is the 'downregulation' of the specificed genes which is responsible for the seem to be contradictory to claim 3 from which they depend because claim 3 specifically recites that the strain *cannot* synthesize capsular polysaccharide and claims 4-7 state that the expression of the capsular polysaccharide is downregulated in

comparison to the native strain thereby implying that not all of the expression is abolished. Clarification and correction is required.

Claims 56-58 are vague and confusing because it is unclear how this additional bleb preparation applies to the bleb preparation of claim 1. Are they conjugated or attached in any manner or is this a composition comprising a mixture of two different blebs? Clarification and correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-8, 14-18 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berthet et al (WO 01/09350 A2).

Berthet et al disclose vaccine compositions comprising non-toxic Gram-negative bleb vaccines, blebs made from *N.meningitidis*, *M.catarrhalis* and *H.influenzae*, for pediatric use. See abstract. The blebs are modified to have down-regulation of immundominant non-protective antigens, up-regulation of protective antigens and detoxification of the Lipid A moiety of LPS. It is particularly exemplified that *N.meningitidis* B strain lacking capsular polysaccharides may be used to isolate the blebs. See claim 14 and page 42 of Berthet. The down-regulation genes include one or more of htrB, msbB and others. See claim 17 and page 23 of the prior art. SiaD is specifically taught as

one of the genes to be down-regulated in claim 20. The down-regulated genes also include one or more selected from the group comprising: porA, porB, opA, opC, pilC, FrpB, etc. See claims 15-16 and page 31 of Berthet. The upregulated genes also include one or more of Hsf, Hap, TbpA. See claims 22 and 27 of Berthet. Berthet teach that other antigens may be conjugated to the bleb preparations, including other antigens from *N.meningitidis*, such as meningococcal capsular polysaccharides from the serotypes A, C, Y or W. See claims 36-39.

Although Berthet teach that other antigens may be conjugated to the bleb preparations, including other antigens from *N.meningitidis*, they do not particularly exemplify the use of LOS of any immunotype, nor do they exemplify that the strain used to make their blebs possessed an L3 LOS immunotype naturally.

Gu et al teach conjugate vaccines comprising detoxified LOS linked to immunogenic carriers for use as vaccines against N.meningitidis. Gu teach that the LOS from N.meningitidis have 12 immunotypes, L1-L12. They teach that L1 to L8 are indentified within groups B and C meningococci. Gu et al specifically teach that the predominant LOS type in the group B disease strains is L3. See column 7, lines 42-43. Gu et al teach that their LOS may be covalently linked to an immunogenic carrier and may be composed of detoxified LOS from different strains and/or immunotypes of N.meningitidis. See Columns 1 and 2. It is taught that LOS may be directly covalently bound to the protein or carrier, for example,

by using the cross linking reagent glutaraldehyde. See column 4, lines 60-65. It is taught that linkers may also be used.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that detoxified LOS could be conjugated/linked to the blebs taught by Berthet et al because Berthet teach that other antigens may be conjugated to the bleb preparations, including other antigens from *N.meningitidis*, and Gu et al teach that detoxified LOS from L1-L8 are very effective vaccine candidates against N.meningitidis. Gu et al teach the use of LOS may be covalently linked to an immunogenic carrier and may be composed of detoxified LOS from different strains and/or immunotypes of N.meningitidis. See Columns 1 and 2. Blebs were well known in the art as immunogenic carriers containing T-helper epitopes which could be used in multivalent vaccines, as evidenced by Berthet. Accordingly, one of ordinary skill in the art, absent evidence to the contrary, would have been motivated to link any one or more of the L1-L8 LOS products taught by Gu et al to the blebs taught by Berthet because doing so would effectively increase the immune response of the compositions taught therein and provide protection against a wider range of bacterial strains. Additionally, the use of an lgtB- strain to produce the blebs would have been obvious to one of ordinary skill in the art since it was well known that this gene makes up the LOS locus and mutants of any of the lgtA-C genes would have resulted in a detoxified preparation. One of ordinary skill would not want to use a bleb preparation from a toxic strain as it could not be

safely used in immunization procedures. The use of adjuvants are taught in both references.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Shanon Foley, can be reached on (571) 272-0898.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645